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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/764,451	01/27/2004	Craig A. Townsend	62732.000152	8691

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EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 09/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/764,451	TOWNSEND ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-31 and 33-48* is/are pending in the application.

4a) Of the above claim(s) *25-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30,31 and 33-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/24/06 has been entered. Claims 25-31 and 33-48 were pending. Applicants amended claim 30, 44 and 45. No claims were added or canceled. Therefore, claim 25-31 and 33-48 are currently pending. In addition, claims 25-29 remain withdraw from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected species and/or invention, there being no allowable generic claim. Therefore, claims 30, 31 and 33-48 are examined on the merits.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

2. All rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 112, first paragraph

3. Claims 30, 31 and 33-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds that inhibit a narrow range of mycobacterium including *tuberculosis*, *bovis* and *avium-intracellulare* "*in vitro*", does not reasonably provide

enablement for the treatment of "any" mycobacterial infection using the full scope of the claimed compounds "*in vivo*" (i.e., a method of treatment). In addition, the specification does not provide support fThe specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". Some of these factors may include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: The claims are broad because they include the treatment of "any" pathogentic mycobacterial-based infection in "any" animal, which would encompass a large number of unrelated etiologies. Consequently, the nature of the invention cannot be fully determined because the invention has not been defined with particularity.

(3 and 5) The state of the prior art and the level of predictability in the art: The prior art

indicates that Applicants' claimed compounds can only be used to inhibit a very narrow range of mycobacterial species "in vitro" including *tuberculosis*, *bovis* and *avium-intracellulare* (e.g., see Jones, P. B.; Parrish, N. M.; Houston, T. A.; Stapon, A.; Bansal, N. P.; Dick J. D.; Townsend, C. A. "A New Class of Antituberculosis Agents" *J. Med. Chem.* **2000**, *43*, 3304-3314, page 3308, column 1, last full paragraph, "The compounds marked with an asterisk in Table 1 [i.e., Applicants' claimed compounds] were also tested against other bacterial strains including *Staphylococcus aureus* (ATC 29213), *Enterococcus faecalis* (ATCC 29212), *Escherichia coli* (ATCC 25922), and *Pseudomonas aeruginosa* (ATCC 27853). ***None exhibited any activity against these bacteria***"; see also page 3309, column 1, paragraph 1, "... these compounds are highly species-specific [i.e., Applicants' claimed compounds], showing no activity against other bacteria including strains of nonpathogentic mycobacteria, such as *M. smegmatis* [i.e., no activity even for other closely related mycobacteria]"; see also Table 1 in specification). In addition, the prior art indicates that only a limited number of alkyl side chains will be biologically active (e.g., see page 3307, column 2, last paragraph, "The most striking structural requirement for these compounds was the length of the side chain ... The difference between a 7-carbon tail (2, MIC > 25 μg/mL) and an 8-carbon tail (3, MIC) 6.25 μg/mL) was dramatic ... 18-carbon tail was ***completely inactive*** against H37Rv").

Finally, where physiological activity is concerned (i.e., the claimed method of treatment), one skilled in the art reasonably would not and properly should not accept *in vitro* results as support for *in vivo* activity. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, Ltd., 927 F.2d 1200, 1216-1217, 18 USPQ2d 1016, 1030 (Fed. Cir.), cert. denied, 502

U.S. 856 (1991). Therefore, to enable one skilled in the art to use a method of treating pathogenic mycobacterial infections *in vivo* based solely on *in vitro* testing, as is the case here, some evidence correlating *in vivo* results to *in vitro* testing at the pertinent time is required. See *In re Brana*, 51 F.3d 1560, 1565 USPQ2d 1437, 1442 (Fed. Cir. 1995)(to enable one skilled in the art to use a clinical method based on preclinical testing, the preclinical testing must be shown to be statistically significant) and *Cross v. Iizuka*, 753 F.2d 1040, 1050-1051, 224 USPQ 739, 747-748 (Fed. Cir. 1985) (preclinical testing activity must at least reasonably correlate to clinical activity to establish utility). In the present case, Applicants have failed to provide any "correlation" between inhibiting a narrow range of slow-growing mycobacteria "in vitro" to treating the currently claimed broad range of organisms "*in vivo*." Furthermore, the prior art indicates (even as of 2001) that the art is in its infancy, the mechanism of action of the claimed compounds is unknown, and that there is logical correlation between these compounds, OSA, and any other classes of compound such as cerulenin and thiolactomycin (e.g., see Parrish et al. "In vitro Activity of a Novel Antimycobacterial Compound, N-Octanesulfonylacetamide, and Its Effects on Lipid and Mycolic Acid Synthesis" Antimicrobial Agents and Chemotherapy 2001, 45(4), 1143-1150, especially paragraph bridging columns 1 and 2 on page 1149, "OSA-mediated inhibition of mycolate synthesis in BCG and MAC may involve an as-yet unidentified enzyme or enzyme system [i.e., mechanism of action is unknown]. In summary, the effects of OSA, cerulenin, and thiolactomycin are mycobacterial species specific and compound specific and inherent differences in the mycolic acid biosynthetic pathway may exist between rapid and slow-growing

mycobacteria"; see also Kurashima, abstract, "***unlike in the case of Mycobacterium tuberculosis, in vitro sensitivity does not correlate with in vivo sensitivity*** [for pulmonary mycobacterium avium-intracellulare complex infections]", please note that a translation of this Japanese document will be provided when it becomes available).

(4) The level of one of ordinary skill: The level of skill required would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants provide only a narrow ranges of examples where their claimed compounds are used "in vitro" to inhibit *tuberculosis*, *bovis* and *avium-intracellulare* (e.g., see specification, Table 1 wherein only MTB, BCG and MAI are disclosed). No "in vivo" data is presented.

(8) The quantity of experimentation needed to make or use the invention base on the content of the disclosure: As a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the Examiner contends that the quantity of experimentation needed to make and or use the invention would be great. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 * n.23 (Fed. Cir. 19991). In this case, Applicants have not provided any working examples that would teach this enormous genus that falls within a highly unpredictable art area. Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the

instant disclosure one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

Response

4. Applicant's arguments directed to the above Enablement rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue that undue experimentation would not be required to practice the currently claimed invention (e.g., amended to "pathogenic mycobacterial infection") as set forth in the Declaration of J. Dick (e.g., see 9/15/06 Response, page 6). According to Dr. James Dick, "the Parrish reference shows that OSA exhibits activity against the pathogenic bacteria M. bovis, M. bovis BCG, M. Kansasii, M. avium complex and M. paratuberculosis, butnot against the rapid growing non-pathogenic bacteria, M. smegmatis, M. fortuitum, M. chelonei, and M. abscessus" (e.g., see Declaration, point 7). In addition, Dr. James Dick states, "Because of the structural similarities between OSA and the compounds of formula I of the invention, these compounds would be expected to exhibit selective activity against slow-growing pathogenic mycobacteria" (e.g., see Declaration, point 8).

This is not found persuasive for the following reasons:

The Declaration under 37 CFR § 1.132 filed 8/24/06 is insufficient to overcome the

rejection of claims 30, 31 and 33-48 based upon 35 U.S.C. 112, first paragraph as set forth in the office action above because:

[1] Applicants' currently amended claims are ambiguous (e.g., see 35 U.S.C. 112, second paragraph rejection below) and, as a result, Applicants' arguments are moot.

[2] Applicants' arguments are not commensurate in scope with the claims. Applicants state, "these compounds would be expected to exhibit selective activity against slow-growning [sic] pathogenic mycobacteria" (e.g., see Declaration, note 7), but the current claims are not limited to treating "slow-growing" pathogenic mycobacteria as purported. To the contrary, the current claims also encompass "fast-growing" pathogenic bacteria. In addition, Dr. James Dick's statement that "*Mycobacterium chelonae*" is "non-pathogenic" (e.g., see Declaration, note 7) is factually mistaken (e.g., see Guerardel et al., "Structural Study of Lipomannan and Pioarabinomannan from *Mycobacterium chelonae*" ***J. Biol. Chem.*** 2002, 277(34), 30635-30648, especially abstract disclosing as an example "*Mycobacterium chelonae* ... [is] a fast growing pathogenic mycobacterial species"). Furthermore, the Parrish et al. reference does not distinguish "pathogenic" from "non-pathogenic" mycobacterium as purported by Applicants (e.g., see 8/24/06 Response, page 6, last paragraph) but, rather, "slow-growing" from "fast-growing" bacteria wherein the mechanism of pathogencity is unknown (e.g., see Parrish et al., page 1149, "Such a target may involve an as-yet-unidentified enzyme or enzyme system present in slow-growing mycobacteria which is not present or inactive in rapid-growing species [i.e., the pathogenic behavior of these two groups is not even distinguished]").

In addition, the "in vitro" evidence (i.e., biological studies for OSA) set forth in the Parrish et al. rejection is also not commensurate scope with Applicants' current

claims/specification (e.g., see claim 30 wherein an R-SO_n-Z-CO-Y genus is disclosed). For example, the currently claimed compounds consist of four structural elements: an acyl derivative, spacer, tetrahedral mimic and hydrophobic tail (e.g., see Jones et al., 3306, column 1, paragraph 1) wherein Parrish et al. set forth that small changes to any one of element may dramatically alter and/or completely negate biological activity (e.g., see Jones et al., page 3306, column 1, last paragraph, "Most of the compounds shown in Table 1, and all active compounds have a single methylene spacer between the tetrahedral mimic and acyl center. The exceptions, 12, 13, and 28-30, are inactive against H37Rv. Thus, a methyl branch at this site, extension to two methylene, or replacement by a readily ionized NH is strongly unfavorable"; see also page 3307, column 2, last paragraph, The most striking structural requirement for these compounds was the length of the side chain ... [compound] 7 with a longer, 18-carbon tail was completely inactive against H37Rv").

[3] Applicants point to a later publication (e.g., Parrish et al., 2001) for the proposition that the genus of compounds disclosed in the current claims is "structurally similar" to OSA (e.g., see Declaration, point 8) and, presumably as a result, the claims would somehow be enabled by this showing. However, it is well settled law that the specification must enable the claimed invention as of its filing date (e.g., see MPEP § 2164.05(a), "Specification Must Be Enabling as of the Filing Date"; see also *In re Budnick*, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976) (In general, if an applicant seeks to use a patent to prove the state of the art for the purpose of the enablement requirement, the patent must have an issue date earlier than the effective filing date of the application.); see also *In re Brandstadter*, 484 F.2d 1395, 1404-1405, 179 USPQ 286, 293-294 (CCPA 1973); *In re Smyth*, 189 F.2d 982, 990, 90 USPQ 106, 112

(CCPA 1951). *Ex post facto* affirmations of practical utility, not previously disclosed in the specification, are irrelevant. *In re Kirk*, 376 F.2d 936, 941-942, 153 USPQ 48, 52-53 (CCPA 1967). Therefore, the Parrish et al. reference and Applicants' declaration addressing this reference are irrelevant in accordance with MPEP § 216405(a) and related case law.

[4] Finally, where physiological activity is concerned (i.e., the claimed method of treatment), one skilled in the art reasonably would not and properly should not accept *in vitro* results as support for *in vivo* activity. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, Ltd., 927 F.2d 1200, 1216-1217, 18 USPQ2d 1016, 1030 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). Therefore, to enable one skilled in the art to use a method of treating pathogenic mycobacterial infections *in vivo* based solely on *in vitro* testing, as is the case here, some evidence correlating *in vivo* results to *in vitro* testing at the pertinent time is required. See *In re Brana*, 51 F.3d 1560, 1565 USPQ2d 1437, 1442 (Fed. Cir. 1995)(to enable one skilled in the art to use a clinical method based on preclinical testing, the preclinical testing must be shown to be statistically significant) and *Cross v. Iizuka*, 753 F.2d 1040, 1050-1051, 224 USPQ 739, 747-748 (Fed. Cir. 1985) (preclinical testing activity must at least reasonably correlate to clinical activity to establish utility). In the present case, Applicants have failed to provide any "correlation" between inhibiting a narrow range of slow-growing mycobacteria "in vitro" to treating the currently claimed broad range of organisms "*in vivo*." Furthermore, the prior art indicates (even as of 2001) that the art is in its infancy, the mechanism of action of the claimed compounds is unknown, and that there is logical correlation between these compounds, OSA, and any other classes of compound such as cerulenin and thiolactomycin (e.g., see Parrish et al. "In vitro Activity of a Novel Antimycobacterial Compound, N-Octanesulfonylacetamide, and Its Effects

on Lipid and Mycolic Acid Synthesis" Antimicrobial Agents and Chemotherapy 2001, 45(4), 1143-1150, especially paragraph bridging columns 1 and 2 on page 1149, "OSA-mediated inhibition of mycolate synthesis in BCG and MAC may involve an as-yet unidentified enzyme or enzyme system [i.e., mechanism of action is unknown]. In summary, the effects of OSA, cerulenin, and thiolactomycin are mycobacterial species specific and compound specific and inherent differences in the mycolic acid biosynthetic pathway may exist between rapid and slow-growing mycobacteria"; see also Kurashima, abstract, "***unlike in the case of Mycobacterium tuberculosis, in vitro sensitivity does not correlate with in vivo sensitivity*** [for pulmonary mycobacterium avium-intracellulare complex infections]").

Accordingly, the Enablement rejection cited above is hereby maintained.

New Rejections

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 30, 31 and 33-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. For **claims 30, 44 and 45**, the phrase "pathogenic mycobacterial infection" is vague and indefinite because it is unclear how an "infection" can "cause a disease" (i.e., an "infection" is the result of a "pathogenic bacteria" entering a host). That is, only living microorganisms like "bacteria", "fungi", etc. can be "pathogenic" (e.g., compare to

original claim 21, "The method of claim 6, wherein the microbially-based infection is caused by pathogenic Mycobacteria sp. [not pathogenic mycobacterial infections]"). Therefore, claims 30, 44 and 45 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
September 14, 2006

JON EPPERSON, PH.D.
PATENT EXAMINER